Looking for the Bistable Behavior

Mathematical Model

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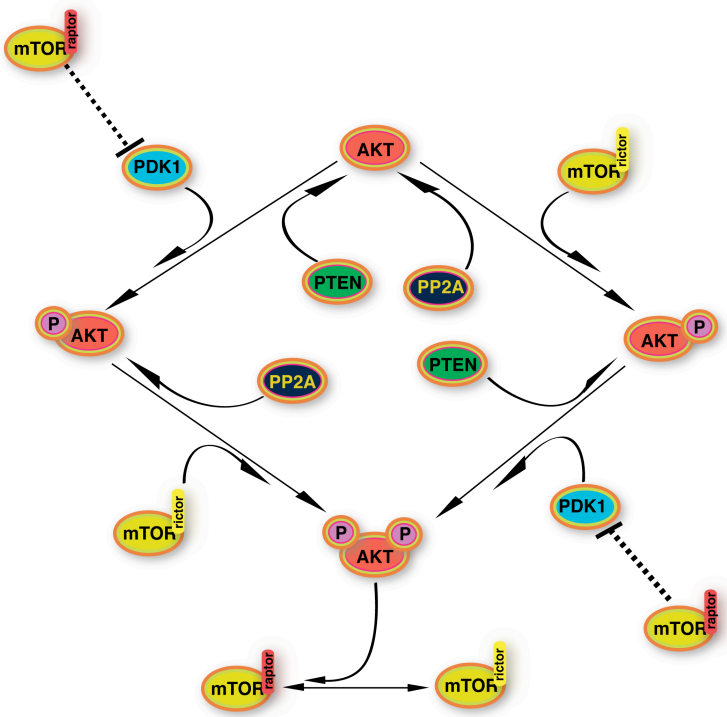
1 Introduction

The purpose of this text is to describe in mathematical terms (via an ordinary differential equations mathematical model) the observed behavior of the pathway which is shown in the following figure:



Remark 1 *It would be convenient to describe in words the network shown in the previous figure. Moreover, it may be desirable to also develop a model written in SBML (possibly using the front end known as CellDesigner, see for instance http://www.systems-biology.org/cd/).*

2 Some previous definitions

Definition 1 PROTEIN *Proteins are large organic compounds made of amino acids arranged in a linear chain and joined together by peptide bonds between the carboxyl and amino groups of adjacent amino acid residues. The sequence of amino acids in a protein is defined by a gene and encoded in the genetic code. Although this genetic code specifies 20 "standard" amino acids plus selenocysteine and - in certain archaea - pyrrolysine, the residues in a protein are sometimes chemically altered in post-translational modification: either before the protein can function in the cell, or as part of control mechanisms. Proteins can also work together to achieve a particular function, and they often associate to form stable complexes.*

Definition 2 ENZYME *nzymes are biomolecules that catalyze (i.e. increase the rates of) chemical reactions. Almost all enzymes are proteins. In enzymatic reactions, the molecules at the beginning of the process are called substrates, and the enzyme converts them into different molecules, the products. Almost all processes in a biological cell need enzymes in order to occur at significant rates. Since enzymes are extremely selective for their substrates and speed up only a few reactions from among many possibilities, the set of enzymes made in a cell determines which metabolic pathways occur in that cell.*

Definition 3 KINASE *In chemistry and biochemistry, a kinase, alternatively known as a phosphotransferase, is a type of enzyme that transfers phosphate groups from high-energy donor molecules, such as ATP, to specific target molecules (substrates); the process is termed phosphorylation (an enzyme that removes phosphate groups from targets is known as a phosphatase).*

Definition 4 *AKT* (protein coding gene) **Official name:** v-akt murine thymoma viral oncogene homolog 1 (Homo sapiens). *The serine[1]-threonine[2] protein kinase encoded by the AKT1 gene is catalytically inactive in serum-starved primary and immortalized fibroblasts. AKT1 and the related AKT2 are activated by platelet-derived growth factor. The activation is rapid and specific, and it is abrogated by mutations in the pleckstrin homology domain of AKT1. It was shown that the activation occurs through phosphatidylinositol 3-kinase. In the developing nervous system AKT is a critical mediator of growth factor-induced neuronal survival. Survival factors can suppress apoptosis in a transcription-independent manner by activating the serine/threonine kinase AKT1, which then phosphorylates and inactivates components of the apoptotic machinery. Multiple alternatively spliced transcript variants have been found for this gene.*

[1]Serine (abbreviated as Ser or S) is an organic compound with the formula $HO_2CCH(NH_2)CH_2OH$. It is one of the 20 naturally occurring proteinogenic amino acids. Its codons are UCU, UCC, UCA, UCG, AGU and AGC. Only the L-stereoisomer appears naturally in proteins. It is one of three amino acid residues that are commonly phosphorylated by kinases during cell signaling in eukaryotes. Phosphorylated serine residues are often referred to as phosphoserine.

[2]Threonine (abbreviated as Thr or T) is an α-amino acid with the chemical formula $HO_2CCH(NH_2)CH(OH)CH_3$. Its codons are ACU, ACA, ACC, and ACG. This essential amino acid is classified as polar. Together with serine and tyrosine, threonine is one of three proteinogenic amino acids bearing an alcohol group. The threonine residue is susceptible to numerous posttranslational modifications. The hydroxy side chain can undergo O-linked glycosylation. In addition, threonine residues undergo phosphorylation through the action of a threonine kinase. In its phosphorylated form, it can be referred to as phosphothreonine.

Definition 5 *PDK1* (protein coding gene) **Official name:** pyruvate dehydrogenase kinase, isozyme 1 (Homo sapiens). *Pyruvate dehydrogenase (PDH) is a mitochondrial multienzyme complex that catalyzes the oxidative decarboxylation of pyruvate and is one of the major enzymes responsible for the regulation of homeostasis of carbohydrate fuels in mammals. The enzymatic activity is regulated by a phosphorylation/dephosphorylation cycle. Phosphorylation of PDH by a specific pyruvate dehydrogenase kinase (PDK) results in inactivation.*

Definition 6 *PP2A* (protein coding) **Official name:** protein phosphatase 2A activator, regulatory subunit 4 (Homo sapiens). *Protein phosphatase 2A is one of the four major Ser/Thr phosphatases and is implicated in the negative control of cell growth and division. Protein phosphatase 2A holoenzymes are heterotrimeric proteins composed of a structural subunit A, a catalytic subunit C, and a regulatory subunit B. The regulatory subunit is encoded by a diverse set of genes that have been grouped into the B/PR55, B'/PR61, and B"/PR72 families. These different regulatory subunits confer distinct enzymatic specificities and intracellular localizations to the holozenzyme. The product of this gene belongs to the B' family. This gene encodes a specific phosphotyrosyl phosphatase activator of the dimeric form of protein phosphatase 2A. Alternative splicing results in multiple transcript variants encoding different isoforms.*

Definition 7 *PTEN* (coding protein gene) **Official name:** phosphatase and tensin homolog (Homo sapiens). *This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It contains a tensin like domain as well as a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. Unlike most of the protein tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates. It negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway.*

Definition 8 *mTOR* (protein coding gene) **Official name:** FK506 binding protein 12-rapamycin associated protein 1 (Homo sapiens). *The protein encoded by this gene belongs to a family of phosphatidylinositol kinase-related kinases. These kinases mediate cellular responses to stresses such as DNA damage and nutrient deprivation. This protein acts as the target for the cell-cycle arrest and immunosuppressive effects of the FKBP12-rapamycin complex.*

Definition 9 *RICTOR*(coding protein gene) **Recommended name:** rapamycin-insensitive companion of mTOR (Homo sapiens). *RICTOR and mTOR are components of a protein complex that integrates nutrient- and growth factor-derived signals to regulate cell growth.*

Definition 10 *RAPTOR* (coding protein gene) **Recommended name:** Regulatory-associated protein of mTOR (Homo sapiens). *Under nutrient-deprived conditions, serves as a negative regulator of mTOR kinase activity. Regulation of the interaction with mTOR is a critical mechanism by which cells coordinate the rate of cell growth and maintenance of cell size with different environmental conditions.*

Definition 11 Rapamicyn *Also known as Sirolimus is s a potent agent antiproliferative that acts at the phases Gl-S of the cellular cycle. It also has antibiotic, antifungal and immunosuppressor activities. As a cellular antiproliferative agent it has being used in coronary stents, providing significant*

reduction in the taxes of hyper proliferation of neointimal intra-stent, that is, the re-obstruction of the coronary artery after stent implant by the unordered and excessive proliferation of endothelial and muscular flat cells in the interior of the stent. Is a relatively new immunosuppressant drug used to prevent rejection in organ transplantation, and is especially useful in kidney transplants. It is a macrolide first discovered as a product of the bacterium Streptomyces hygroscopicus in a soil sample from an island called Rapa Nui, better known as Easter Island. It is marketed under the trade name Rapamune by Wyeth. Interestingly, sirolimus was originally developed as an antifungal agent. However, this was abandoned when it was discovered that it had potent immunosuppressive and antiproliferative properties.

3 The Model

- Michealis-Menten reaction:

$$\frac{d[P]}{dt} = \alpha[E_0]\frac{[S]}{K_m + [S]} = V_{\max}\frac{[S]}{K_m + [S]},$$

  where:

$$V_{\max} := \alpha[E_0],$$

  with:

  - $[E_0]$ is the total concentration of enzyme;
  - $[S]$ is the concentration of substrate;
  - α is the catalytic constant;
  - K_m is the Michaelis constant.

- The equation for $[rictor]$:

$$\frac{d[rictor]}{dt} = -\alpha_{\text{pAKT\_rictor}}\frac{[rictor][pAKT]}{K_{\text{pAKT\_rictor}} + [rictor]} + \beta_{\text{raptor\_2\_rictor}}[raptor]$$

- The equation for $[pAKT]$:

$$\begin{aligned}\frac{d[pAKT]}{dt} &= \alpha_{\text{rictor\_AKT}}\frac{[rictor][AKT]}{K_{\text{rictor\_AKT}} + [AKT]} \\ &\quad -\alpha_{\text{PP2A\_pAKT}}\frac{[PP2A][pAKT]}{K_{\text{PP2A\_pAKT}} + [pAKT]} \\ &\quad -\alpha_{\text{PDK1p\_AKT}}\frac{[PDK1p][pAKT]}{K_{\text{PDK1p\_AKT}} + [pAKT]} \\ &\quad +\alpha_{\text{PP2A\_AKTp}}\frac{[PP2A][pAKTp]}{K_{\text{PP2A\_AKTp}} + [pAKTp]} \\ &\quad +\alpha_{\text{PTEN\_AKTp}}\frac{[PTEN][pAKTp]}{K_{\text{PTEN\_AKTp}} + [pAKTp]}\end{aligned}$$

- The equation for $[AKTp]$:

$$\begin{aligned}
\frac{d[AKTp]}{dt} &= \alpha_{\text{PDK1p_AKT}} \frac{[PDK1p][AKT]}{K_{\text{PDK1p_AKT}} + [AKT]} \\
&\quad -\alpha_{\text{PP2A_AKTp}} \frac{[PP2A][AKTp]}{K_{\text{PP2A_AKTp}} + [AKTp]} \\
&\quad -\alpha_{\text{rictor_AKT}} \frac{[rictor][AKTp]}{K_{\text{rictor_AKT}} + [AKTp]} \\
&\quad +\alpha_{\text{PP2A_AKTp}} \frac{[PP2A][pAKTp]}{K_{\text{PP2A_AKTp}} + [pAKTp]} \\
&\quad -\alpha_{\text{PTEN_AKTp}} \frac{[PTEN][AKTp]}{K_{\text{PTEN_AKTp}} + [AKTp]}
\end{aligned}$$

- The equation for $[AKT]$:

$$\begin{aligned}
\frac{d[AKT]}{dt} &= -\alpha_{\text{PDK1p_AKT}} \frac{[PDK1p][AKT]}{K_{\text{PDK1p_AKT}} + [AKT]} \\
&\quad +\alpha_{\text{PP2A_pAKT}} \frac{[PP2A][pAKT]}{K_{\text{PP2A_pAKT}} + [pAKT]} \\
&\quad -\alpha_{\text{rictor_AKT}} \frac{[rictor][AKT]}{K_{\text{rictor_AKT}} + [AKT]} \\
&\quad +\alpha_{\text{PP2A_AKTp}} \frac{[PP2A][AKTp]}{K_{\text{PP2A_AKTp}} + [AKTp]} \\
&\quad +\alpha_{\text{PTEN_AKTp}} \frac{[PTEN][AKTp]}{K_{\text{PTEN_AKTp}} + [AKTp]}
\end{aligned}$$

- The equation for $[pAKTp]$:

$$\begin{aligned}\frac{d[pAKTp]}{dt} &= \alpha\_\text{PDK1p\_AKT}\frac{[PDK1p][pAKT]}{K_\text{PDK1p\_AKT}+[pAKT]} \\ &+\alpha_\text{rictor\_AKT}\frac{[rictor][AKTp]}{K_\text{rictor\_AKT}+[AKTp]} \\ &-\alpha_\text{PP2A\_AKTp}\frac{[PP2A][pAKTp]}{K_\text{PP2A\_AKTp}+[pAKTp]} \\ &-\alpha_\text{PP2A\_AKTp}\frac{[PP2A][pAKTp]}{K_\text{PP2A\_AKTp}+[pAKTp]} \\ &-\alpha_\text{PTEN\_AKTp}\frac{[PTEN][pAKTp]}{K_\text{PTEN\_AKTp}+[pAKTp]}\end{aligned}$$

- The equation for $[PDK1]$:

$$\frac{d[PDK1p]}{dt} = -\alpha_\text{raptor\_PDK1p}\frac{[raptor][PDK1p]}{K_\text{raptor\_PDK1p}+[PDK1p]} + \beta_\text{PDK1\_2\_PDK1p}[PDK1]$$

- The equation for $[raptor]$:

$$[raptor] = \text{mTOR\_total} - [rictor]$$

- The equation for $[PDK1p]$:

$$[PDK1] = \text{PDK1\_total} - [PDK1p]$$

3.1 Parameters

- Catalytic and Michaelis constants:

Catalytic contants			Michaelis constants		
$\alpha_\text{pAKT\_rictor}$	=	10	$K_\text{pAKT\_rictor}$	=	10
$\alpha_\text{rictor\_AKT}$	=	20	$K_\text{rictor\_AKT}$	=	5
$\alpha_\text{PP2A\_pAKT}$	=	4	$K_\text{PP2A\_pAKT}$	=	0.1
$\alpha_\text{PDK1p\_AKT}$	=	20	$K_\text{PDK1p\_AKT}$	=	10
$\alpha_\text{PP2A\_AKTp}$	=	1	$K_\text{PP2A\_AKTp}$	=	0.1
$\alpha_\text{PTEN\_AKTp}$	=	1	$K_\text{PTEN\_AKTp}$	=	0.25
$\alpha_\text{raptor\_PDK1p}$	=	10	$K_\text{raptor\_PDK1p}$	=	10

- β-constants:

$$\begin{aligned}\beta_\text{raptor\_2\_rictor} &= 1; \\ \beta_\text{PDK1\_2\_PDK1p} &= 5.\end{aligned}$$

3.2 Initial conditions

In what follows $[\cdot]_0$ to stand for the initial value of concentration $[\cdot]$.

Initial concentrations	Value
$[rictor]_0$	0.0
$[pAKT]_0$	0.0
$[AKTp]_0$	0.0
$[AKT]_0$	100.0
$[pAKTp]_0$	0.0
$[PDK1p]_0$	50.0

3.3 Constant concentrations

$$[PP2A] = [PP2A]_0 = 150.0;$$

$$[PTEN] = [PTEN]_0 = 200.$$

3.4 The values of mTOR_total and PDK1_total

$$\text{mTOR\_total} = 100;$$

$$\text{PDK1\_total} = 100.$$

4 Simplifying

We can simplify the previous equations taking into account the following definition of the Michaelis-Menten function:

$$f_{\text{MM}}^{(K_M,\alpha)}([E_0],[S]) := \alpha[E_0]\frac{[S]}{K_m + [S]}.$$

In order to make easy the writing of the set of equations, in a computer simulation software, the following redefinition of the variables and parameters will be respected in the sequel:

new name	old name	value or in. cond.	new name	old name	value or in. cond.
a_1	$\alpha_{\text{pAKT\_rictor}}$	10	K_1	$K_{\text{pAKT\_rictor}}$	10
a_2	$\alpha_{\text{rictor\_AKT}}$	20	K_2	$K_{\text{rictor\_AKT}}$	5.0
a_3	$\alpha_{\text{PP2A\_pAKT}}$	4	K_3	$K_{\text{PP2A\_pAKT}}$	0.1
a_4	$\alpha_{\text{PDK1p\_AKT}}$	20	K_4	$K_{\text{PDK1p\_AKT}}$	10.0
a_5	$\alpha_{\text{PP2A\_AKTp}}$	1	K_5	$K_{\text{PP2A\_AKTp}}$	0.1
a_6	$\alpha_{\text{PTEN\_AKTp}}$	1	K_6	$K_{\text{PTEN\_AKTp}}$	0.25
a_7	$\alpha_{\text{raptor\_PDK1p}}$	10	K_7	$K_{\text{raptor\_PDK1p}}$	10.0
x_1	$[rictor]$	0.0	$\overline{x_8}$	$[PP2A]$	150.0
x_2	[PDK1p]	50.0	$\overline{x_9}$	$[PTEN]$	200.0
x_3	$[AKTp]$	0.0	u_1	mTOR_total	100.0
x_4	$[AKT]$	100.0	u_2	PDK1_total	100.0
x_5	$[pAKTp]$	0.0	b_1	$\beta_{\text{raptor\_2\_rictor}}$	1.0
x_6	$[pAKT]$	0.0	b_2	$\beta_{\text{PDK1\_2\_PDK1p}}$	5.0

The model is then given as follows:

$$
\begin{aligned}
\dot{x}_1 &= -f_{MM}^{(K_1,a_1)}(x_6,x_1) - b_1x_1 + b_1u_1;\\
\dot{x}_2 &= f_{MM}^{(K_7,a_7)}(x_1,x_2) - b_2x_2 - a_7\tfrac{x_2}{K_7+x_2}u_1 + b_2u_2;\\
\dot{x}_3 &= f_{MM}^{(K_4,a_4)}(x_2,x_4) - f_{MM}^{(K_5,a_5)}(\overline{x_8},x_3) - f_{MM}^{(K_2,a_2)}(x_1,x_3) + f_{MM}^{(K_5,a_5)}(\overline{x_8},x_5) - f_{MM}^{(K_6,a_6)}(\overline{x_9},x_3);\\
\dot{x}_4 &= -f_{MM}^{(K_4,a_4)}(x_2,x_4) + f_{MM}^{(K_3,a_3)}(\overline{x_8},x_6) - f_{MM}^{(K_2,a_2)}(x_1,x_4) + f_{MM}^{(K_5,a_5)}(\overline{x_8},x_3) + f_{MM}^{(K_6,a_6)}(\overline{x_9},x_3);\\
\dot{x}_5 &= f_{MM}^{(K_4,a_4)}(x_2,x_6) + f_{MM}^{(K_2,a_2)}(x_1,x_3) - \underbrace{f_{MM}^{(K_5,a_5)}(\overline{x_8},x_5)}_{A} - \underbrace{f_{MM}^{(K_5,a_5)}(\overline{x_8},x_5)}_{B} - f_{MM}^{(K_6,a_6)}(\overline{x_9},x_5)\\
\dot{x}_6 &= f_{MM}^{(K_2,a_2)}(x_1,x_4) - f_{MM}^{(K_3,a_3)}(\overline{x_8},x_6) - f_{MM}^{(K_4,a_4)}(x_2,x_6) + f_{MM}^{(K_5,a_5)}(\overline{x_8},x_5) + f_{MM}^{(K_6,a_6)}(\overline{x_9},x_5).
\end{aligned}
$$

Remark 2 *Are elements A and B really identical?*